
Retinoic Acid functions as a key GABAergic differentiation signal in the Basal Ganglia.

Journal: PLoS Biol

Publication Year: 2011

Authors: Christina Chatzi, Thomas Brade, Gregg Duester

PubMed link: 21532733

Funding Grants: Retinoic Acid-FGF Antagonism during Motor Neuron Differentiation of Human ES Cells

Public Summary:

The vitamin A metabolite retinoic acid has been implicated as an important signaling molecule needed for development of the central nervous system. Previous studies have demonstrated clear roles for retinoic acid in regulating genes needed for generation of motor neurons in the hindbrain and spinal cord, but the role of retinoic acid in the forebrain has remained elusive. Here, we investigate mice lacking the ability to metabolize vitamin A to retinoic acid in the forebrain. Although no defects were observed in generation of cortical neurons that process most information in the forebrain, we did observe a serious deficiency of one type of neuron that provides inhibitory input to cortical neurons, i.e. GABAergic neurons. Our studies demonstrate that retinoic acid is required for specific forebrain neurons to activate an enzyme that converts glutamate to the inhibitory neurotransmitter GABA. We also found that retinoic acid treatment of human embryonic stem cells was able to stimulate production of GABAergic neurons. Deficiencies in GABAergic neurons have been associated with several neurological disorders including Huntington's disease, autism, schizophrenia, bipolar depression, and epilepsy. Knowledge of how GABAergic neurons are generated may aid efforts to treat these diseases.

Scientific Abstract:

Although retinoic acid (RA) has been implicated as an extrinsic signal regulating forebrain neurogenesis, the processes regulated by RA signaling remain unclear. Here, analysis of retinaldehyde dehydrogenase mutant mouse embryos lacking RA synthesis demonstrates that RA generated by *Raldh3* in the subventricular zone of the basal ganglia is required for GABAergic differentiation, whereas RA generated by *Raldh2* in the meninges is unnecessary for development of the adjacent cortex. Neurospheres generated from the lateral ganglionic eminence (LGE), where *Raldh3* is highly expressed, produce endogenous RA, which is required for differentiation to GABAergic neurons. In *Raldh3*^{-/-} embryos, LGE progenitors fail to differentiate into either GABAergic striatal projection neurons or GABAergic interneurons migrating to the olfactory bulb and cortex. We describe conditions for RA treatment of human embryonic stem cells that result in efficient differentiation to a heterogeneous population of GABAergic interneurons without the appearance of GABAergic striatal projection neurons, thus providing an in vitro method for generation of GABAergic interneurons for further study. Our observation that endogenous RA is required for generation of LGE-derived GABAergic neurons in the basal ganglia establishes a key role for RA signaling in development of the forebrain.

Source URL: <http://www.cirm.ca.gov/about-cirm/publications/retinoic-acid-functions-key-gabaergic-differentiation-signal-basal-ganglia>